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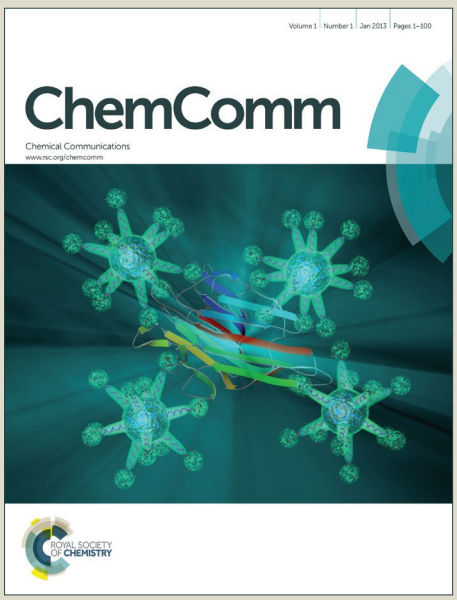

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Highly Stereoselective Cyclopropanation of Diazo Weinreb Amides Catalyzed by Chiral Ru(II)-*Amm*-Pheox Complexes

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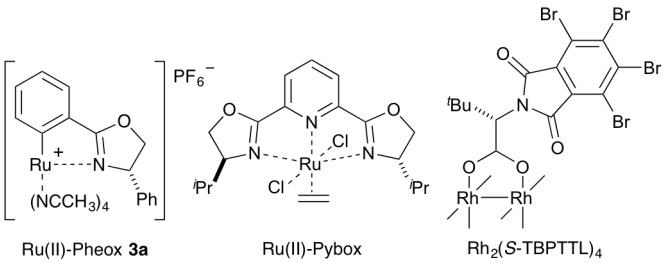
The first highly stereoselective cyclopropanation of diazo Weinreb amides with olefins was accomplished using chiral Ru(II)-*Amm*-Pheox complex 7a to give the corresponding chiral cyclopropyl Weinreb amides in high yields (up to 99%) with excellent diastereoselectivities (up to 99:1 dr) and enantioselectivities (up to 96% ee).

Chiral cyclopropane derivatives are valuable structural motifs found in numerous natural products with diverse biological activities.[1] Thus, during the past two decades, the development of synthetic methodologies toward chiral cyclopropane compounds has attracted much attention and the transition-metal-catalyzed asymmetric cyclopropanation of olefins with diazoacetates is widely recognized as one of the more powerful methods in terms of highly stereoselective synthesis.[2] In contrast to the excellent results obtained with diazoacetates,[3] diazoacetamides are rarely used as a carbene source because of the low electrophilicity and steric hindrance of the resulting metal-carbene intermediate.[4] This prompted us to explore the asymmetric cyclopropanation of olefins with various diazoacetamides, namely, diazo Weinreb amides, because the resulting cyclopropanes are potentially useful synthetic intermediates that can be easily converted to the corresponding aldehydes, ketones, and alchohols.[5] Therefore, we initially prepared diazo Weinreb amides, such as *N*-methoxy-*N*-methyl diazoacetamide (MMD) **2a**,[6] the novel *N*-benzyl-*N*-methoxy diazoacetamide (BMD) **2b**, and *N*-acetoxy-*N*-methyl diazoacetamide (AMD) **2c**, according to the Fukuyama method.[7]

In our previous studies Ru(II)-Pheox complex **3a** proved to be an efficient catalyst for inter- and intramolecular cyclopropanations of various diazoacetates.[8] Hence, we decided to use **3a** for the asymmetric cyclopropanation of diazo Weinreb amides **2** (Table 1). The reaction of simple diazo Weinreb amide MMD **2a** proceeded smoothly at room temperature to afford the desired cyclopropane product **4a** in low yield with moderate stereoselectivity (entry 1). Investigation of the effect of temperature revealed that −30 °C is the most efficient for the cyclopropanation reaction, giving the corresponding product in high yield (80%) with high enantioselectivity (90% ee), albeit with low *trans/cis* ratio (83:17 dr) (entry 4). The use of bulky diazo Weinreb amide BMD **2b** did not show any improvement (entry 6). On the basis of the successful use

Table 1 Screening of various diazo Weinreb amides and catalysts[a]



Entry	Cat.	R	Diazo **2**	Temp (°C)	Yield (%)[b]	*trans*/*cis*[c]	*trans* ee (%)[d]
1	**3a**		MMD **2a**	RT	58	87:13	80
2	**3a**		MMD **2a**	0	67	79:21	80
3	**3a**		MMD **2a**	−10	74	89:11	87
4	**3a**		MMD **2a**	−30	80	83:17	90
5	**3a**		MMD **2a**	−50	71	42:58	86
6	**3a**		BMD **2b**	−30	70	80:20	80
7	**3a**		**AMD 2c**	**−30**	**81**	**99:1**	**85**
8[e]	Rh(II)-Pybox		AMD **2c**	−30	0	–	–
9[e]	Rh(II)-Pybox		AMD **2c**	45	18	85:15	53
10[e]	Rh_2(*S*-TBPTTL)$_4$		AMD **2c**	−30	0	–	–
11[e]	Rh_2(*S*-TBPTTL)$_4$		AMD **2c**	RT	20	71:29	26
12[e]	$Rh_2(OAc)_4$		AMD **2c**	RT	0	–	–

[a] Reaction conditions: diazoacetamide **2** diluted in CH_2Cl_2 was slowly added over 10 h by using a syringe pump. [b] Isolated yield. [c] Determined by NMR. [d] Determined by chiral HPLC analysis. [e] 5 mol% of catalyst was used.

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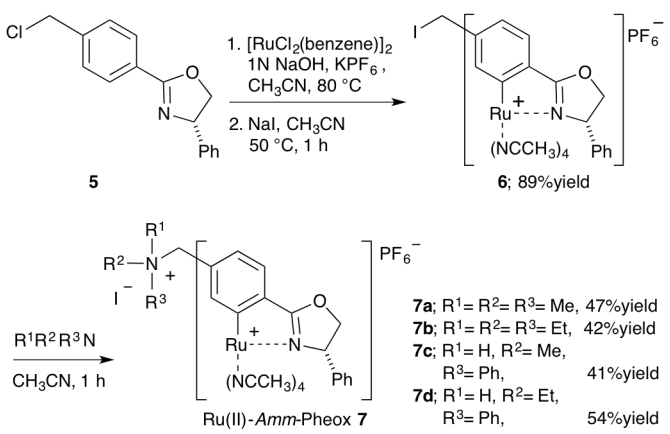
of functionalized diazoacetates for highly stereoselective cyclopropanations,[9] functionalized diazo Weinreb amide **2c** was also investigated and was found to be crucial for the *trans*-selectivity: the corresponding cyclopropylamide **4c** was obtained in 99:1 dr, albeit with low enantioselectivity (85% ee) (entry 7). Surprisingly, the cyclopropanation with commonly used catalysts, such as $Rh_2(OAc)_4$, Ru(II)-Pybox[10] and Rh_2(*S*-TBPTTL)$_4$[11] proceeded with low yields and poor enantioselectivities (products resulting from the dimerization of the diazo compound were mainly observed)(entries 8–12).

In order to improve the enantioselectivity, the Ru(II)-Pheox **3a** catalyst was modified in terms of electron density (catalysts **3b–d**) and bulkiness (catalysts **7a–d**). An internal quaternary ammonium unit is featured in these complexes, on account of the enhanced reaction rate and selectivity observed by Jeffery and co-workers upon addition of quaternary ammonium salts as additives.[12] Catalyst **7a–d** were prepared as shown in Scheme 1. At first, we successfully synthesized Ru(II)-(iodomethyl)phenyl-Pheox complex **6** from (chloromethyl)phenyl-Pheox ligand **5** in 89% yield for two steps. Treatment of **6** with appropriate tertiary amines in CH_3CN afforded the desired Ru(II)-*Amm*-Pheox catalysts **7a–d** in moderate yields (41–54%).



Scheme 1 Synthesis of Ru(II)-*Amm*-Pheox complexes

Screening of various Ru(II)-Pheox **3** and Ru(II)-*Amm*-Pheox **7** catalysts is shown in Table 2. As a result, we found that the enantioselectivity could be increased to 89% ee by using Ru(II)-Pheox catalyst **3c**, which bears a CF_3 electron-withdrawing group (entry 3). Surprisingly, the bulky Ru(II)-*Amm*-Pheox **7a** exhibited higher activity and enantioselectivity as compared with simple Ru(II)-Pheox **3**, giving the corresponding product in high yield (98%) with excellent diastereoselectivity (98:2 dr) and high enantioselectivity (92% ee) (entry 5). To the best of our knowledge, this is the first report on the highly stereoselective cyclopropanation reaction of diazo Weinreb amide derivatives. It is noteworthy that increasing the bulkiness of the quaternary ammonium unit on the Ru(II)-*Amm*-Pheox **7** had negative effects on the yield and the enantioselectivity of the reaction (entries 6–8).

Table 2 Screening of various Ru(II)-Pheox type catalysts[a] View Article Online
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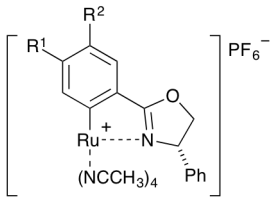
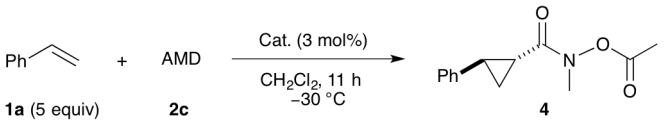


3a; R^1= H, R^2= H
3b; R^1= H, R^2= OMe
3c; R^1= H, R^2= CF_3
3d; R^1= NO_2, R^2= H



1a (5 equiv) **2c** **4**

Entry	Cat.	Yield (%)[b]	*trans/cis*[c]	*trans* ee (%)[d]
1	Ru(II)-Pheox **3a**	81	99:1	85
2	Ru(II)-Pheox **3b**	95	99:1	78
3	Ru(II)-Pheox **3c**	89	99:1	89
4	Ru(II)-Pheox **3d**	83	86:14	77
5	Ru(II)-*Amm*-Pheox **7a**	**98**	**98:2**	**92**
6	Ru(II)-*Amm*-Pheox **7b**	91	98:2	92
7	Ru(II)-*Amm*-Pheox **7c**	83	98:2	89
8	Ru(II)-*Amm*-Pheox **7d**	87	97:3	86

[a] Reaction conditions: AMD **2c** diluted in CH_2Cl_2 was slowly added over 10 h by using a syringe pump. [b] Isolated yield. [c] Determined by NMR. [d] Determined by chiral HPLC analysis.

Encouraged by these results, we investigated the cyclopropanation of diazo Weinreb amide AMD **2c** with various olefins using Ru(II)-*Amm*-Pheox **7a**. The obtained results are summarized in Table 3. The reaction of styrene derivatives bearing an electron-donating group at the para position showed a higher enantioselectivity as compared with those with an electron-donating substituent at the ortho or meta position (entries 2–4). Namely, the highest enantioselectivity (96% ee) was obtained for the styrene bearing a para-methoxy substituent (entry 5). An electron-withdrawing substituted styrene could be easily cyclopropanated with AMD **2c** without any significant loss in catalytic activity and stereoselectivity (entry 6). On the other hand, the cyclopropanation of α-methyl substituted styrene afforded the desired product with moderate enantioselectivity (74% ee) but in high yield and high *trans/cis* ratio (entry 7). In addition, Ru(II)-*Amm*-Pheox **7a** proved to be effective for the asymmetric cyclopropanation of sterically demanding *tert*-butyl vinyl ether and *N*-vinylcarbazole to provide the corresponding cyclopropane products in high yields with excellent diastereo- and enantioselectivities (entries 8 and 9). However, moderate enantioselectivity was obtained when *N*-methyl-*N*-vinylacetamide was used as olefinic substrate (76% ee) (entry 10).

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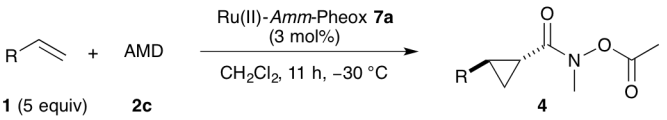
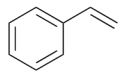
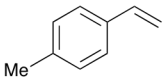
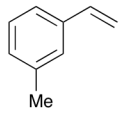
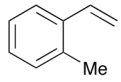
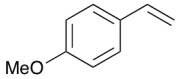
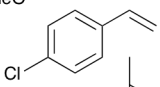
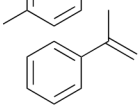
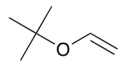
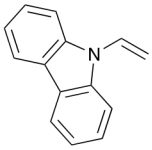
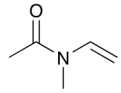
Table 3 Asymmetric cyclopropanation of various olefins[a]

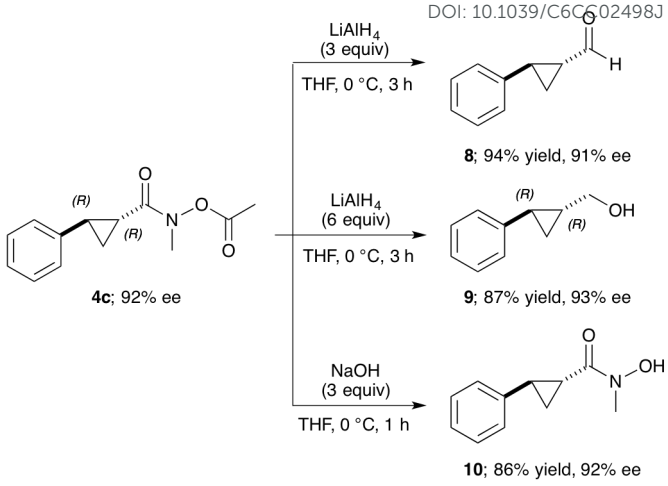


1 (5 equiv) **2c** **4**

Entry	Olefin **1**	Yield (%)[b]	*trans*/*cis*[c]	*trans* ee (%)[d]
1		98	98:2	92
2		96	96:4	94
3		94	99:1	92
4		97	99:1	90
5		93	93:7	96
6		94	99:1	92
7		96	96:4	74
8		95	99:1	91
9		99	99:1	96
10		86	91:9	76

[a] Reaction conditions: AMD **2c** diluted in CH_2Cl_2 was slowly added over 10 h by using a syringe pump. [b] Isolated yield. [c] Determined by NMR. [d] Determined by chiral HPLC analysis.

In order to demonstrate the advantage of using diazo Weinreb amides as carbene source for the asymmetric cyclopropanation, we investigated the synthetic transformations of the obtained cyclopropane products (Scheme 2). Chiral cyclopropyl Weinreb amide **4c** can easily undergo reduction with $LiAlH_4$ under appropriate conditions to form the corresponding chiral (1*R*,2*R*)-aldehyde **8** and (1*R*,2*R*)-alcohol **9** in high yields with high diastereo- and enantioselectivities. In addition, treatment of **4c** with NaOH in THF afforded chiral cyclopropyl Weinreb amide **10** in high yield (86%) and unaltered enantioselectivity (92% ee). Since the (1*R*,2*R*) configuration of alcohol **9** was confirmed by the comparison of its optical rotation,[13] the absolute configuration of cyclopropyl Weinreb amide **4c** was also determined to be (1*R*,2*R*).



Scheme 2 Synthetic transformations of cyclopropyl Weinreb amide **4c**

To further demonstrate the utility of the obtained chiral products, we next investigated the arylation of chiral cyclopropyl Weinreb amide **4c** with Grignard reagent PhMgBr for the formation of chiral cyclopropyl ketone **11**. Unfortunately, the desired product was obtained in low yield and many byproducts were observed. On the other hand, the arylation reaction of chiral cyclopropyl Weinreb amide **4a** proceeded smoothly to provide the desired chiral cyclopropyl ketone **11** in 89% yield with high enantioselectivity (90% *trans* ee) (Scheme 3).

Scheme 3 Synthetic transformation of cyclopropyl Weinreb amide **4a** to ketone **11**

We envisioned that the high level of diastereocontrol achieved with this catalytic system could be attributed to the formation of a bulky seven-membered ring by coordination of the acetoxy carbonyl group with the Ru metal center, which prevented a *cis*-selective approach of the styrene as described in previous reports.[9] These results clearly indicate the importance of using a carbonyl-functionalized diazo Weinreb amide as carbene source to achieve a highly *trans*-selective cyclopropanation. On the other hand, we speculate that the high enantioselectivity achieved with this catalytic system might be attributed to the bulky quaternary ammonium unit, which prevents a (1*S*,2*S*)-selective approach of the styrene from the *re-face* (the chiral environment of the phenyl group might prevent the styrene closing in from the *si-face*) (Scheme 4).

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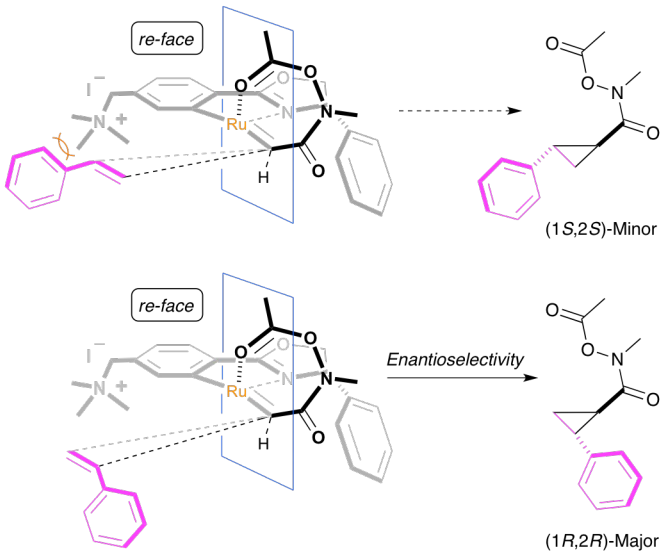

Scheme 4 A plausible mechanism for highly enantioselective cyclopropanation

In conclusion, we successfully developed of the first highly stereoselective cyclopropanation of diazo Wienreb amides with olefins using chiral Ru(II)-Pheox-type catalysts. Ru(II)-*Amm*-Pheox complex **7a** featuring an internal quaternary ammonium unit exhibited obviously higher activity and enantioselectivity as compared with previously described Ru(II)-Pheox complex **3**, to afford the corresponding chiral cyclopropyl Weinreb amides in high yields (up to 99%) with excellent diastereoselectivities (up to 99:1 dr) and enantioselectivities (up to 96% ee). In addition, the use of acetoxy-functionalized diazoacetamide AMD as a carbene source was found to be crucial for the high *trans*-selectivity of the cyclopropanation reaction. Moreover, the obtained chiral Weinreb amides were readily converted to various useful synthetic intermediates, such as alcohols, ketones, and aldehydes, in one step and without any loss of enantioselectivity.

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